REMARKS

Entry of the foregoing amendments and favorable consideration of the subject application are respectfully requested in view of the following comments.

The claims have been amended to conform to the election made January 11, 2008 and in response to the objections and rejections made in the current Office Action.

Specifically, references to fibrate type cholesterol lowering agents in claims 1 and 2 have been deleted. In addition, claim 1 has been amended to properly recite the invention as "comprising" the compound of general formula (I) and cholesterol biosynthesis inhibitors, recognizing that such agents routinely include additives and excipients such as lubricants, binders, fillers, buffers, emulsifiers, preservatives, etc., as set forth in the specification at page 17. In addition, the claims have been amended to correct grammatical and idiomatic errors and to conform with U.S. practice. In particular, claims 4, 5, 9 and 11 have been amended to recite the agent of their respective parent claim where the compound of general formula (I) is a specific compound as identified by the formula given in the respective claim. In addition, claims 6, 13, 15, 16, 18 and 19 have been amended to eliminate the confusing "use" language and to correctly identify the serum cholesterol lowering agent as characterized by the cholesterol biosynthesis inhibitor being at least one chosen from the listed group.

Applicants respectfully submit that no new matter has been added by the foregoing amendments and that the application is in condition for allowance.

Priority

Responsive to the examiner's notice that English translation of the Japanese language priority document, Application No. 2003-185171, has not yet been filed, Applicants herewith provide the required translation together with the translator's verification.

Claim Objections

The examiner has objected to claim 2 under 37 CFR 1.75 as being a substantial duplicate of claim 1, contending that the claims differ in the use of the word "combination" versus the word "mixture".

Applicants respectfully submit that, in the present invention, "combination" and "mixture" are substantially different in that "combination" refers to the compound of general formula (I) and the cholesterol biosynthesis inhibitors being together and may include them as separate entities administered individually, successively or simultaneously, whereas "mixture" refers to the compound of general formula (I) and the cholesterol biosynthesis inhibitors intermixed to form a single entity for dosing. In this sense, the "combination" of claim 1 is a broader recitation of the serum cholesterol lowering agent or preventive

or therapeutic agent of the present invention which includes all forms in which that agent may be presented, whereas the mixture of claim 2 constitutes a single preferred form which is specific to a physical mixing of the two recited elements of the serum cholesterol lowering agent or preventive or therapeutic agent of the present invention. Thus, claim 2 and those claims depending therefrom present a limitation of the invention of claim 1 to a specific and preferred form.

Applicants respectfully submit that, in view of the above, the examiner's objection is without merit and should be withdrawn.

Rejection Under 35 U.S.C. §112 second paragraph

The Office Action rejects claims 1, 2, 4-6, 9, 11, 13, 15, 16, 18 and 19 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The office action states:

"The claims are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

Claim 4 is drawn to the agent of claim 1 and consists of a compound of the given formula. The agent of claim 1 consists of both a compound of formula (I) and a cholesterol biosynthesis inhibitor. There is a lack of antecedent basis for this limitation in the claim; the agent cannot consist of a combination of a compound of formula (I) and a cholesterol biosynthesis inhibitor

and also consist of only a compound of the given formula. "Consisting of" is closed language which does not permit the inclusion of any other elements into the composition. Claims 5, 9 and 11 are similarly rejected.

Claim 6 is drawn to the agent of claim 1 "characterized by the use of" specific types of cholesterol biosynthesis inhibitors. Claim 1 is a product claim and it is unclear what is meant by "use". The claim is interpreted to mean that at least one cholesterol biosynthesis inhibitor must be present in the composition of claim 1 and must be a HMG-CoA reductase inhibitor, squalene synthase inhibitor, or a squalene epoxydase inhibitor. Similarly claims 13, 15, 16, 18 and 19 are rejected. Clarification is requested."

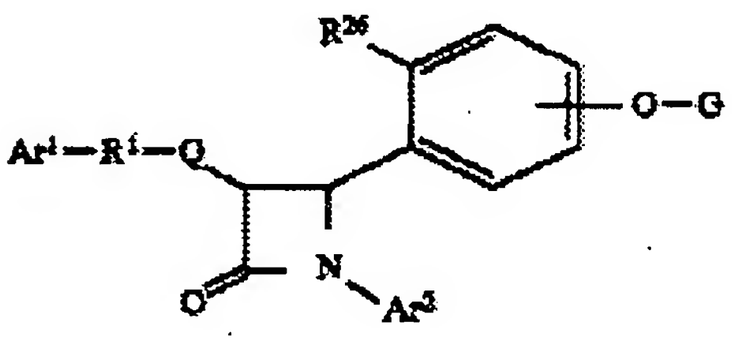
In view of the foregoing amendments to the claims correcting grammatical and idiomatic errors and placing them in condition which conforms with U.S. practice, Applicants respectfully submit that the grounds for rejection under 35 U.S.C. §112, second paragraphs have been overcome. Claims 4, 5, 9 and 11 now properly identify the compound represented by general formula (I) as the specific formula recited in the respective claims and claims 6, 13, 15, 16, 18 and 19, now properly identify the serum cholesterol lowering agent of the invention as characterized by the cholesterol biosynthesis inhibitor being at least one chosen from the listed group.

Rejection of Claims Under 35 U.S.C. §103(a)

The Office Action rejects claims 1, 2, 4-6, 9, 11, 13, 15, 16, 18 and 19 under 35 U.S.C. § 103(a) as being unpatentable over Yumibe et al. (U.S. 5,756,470, May 26, 1998) and Tomiyama et al. (U.S. 2004/0063929, April 1, 2004, PTO-1449 submitted April 25,

2006, English equivalent of WO02/066464, published August 29, 2002). The Office Action states:

> "Yumibe et al teaches a combination of a cholesterol biosynthesis inhibitor and a β-lactam cholesterol absorption inhibitor for lowering cholesterol and treating or preventing atherosclerosis [see abstract]. The combination of a beta-lactam cholesterol absorption inhibitor and HMG-CoA reductase inhibitor results in a greater decrease in plasma cholesterol than either agent alone [column 2, lines 11-20]. Suitable cholesterol biosynthesis inhibitors include HMG CoA reductase inhibitors, squalene synthesis inhibitors, and squalene epoxidase inhibitors [column 2, lines 51-63 and claim 20]. The genus of compounds taught by Yumibe et al. is as follows [column 2]:

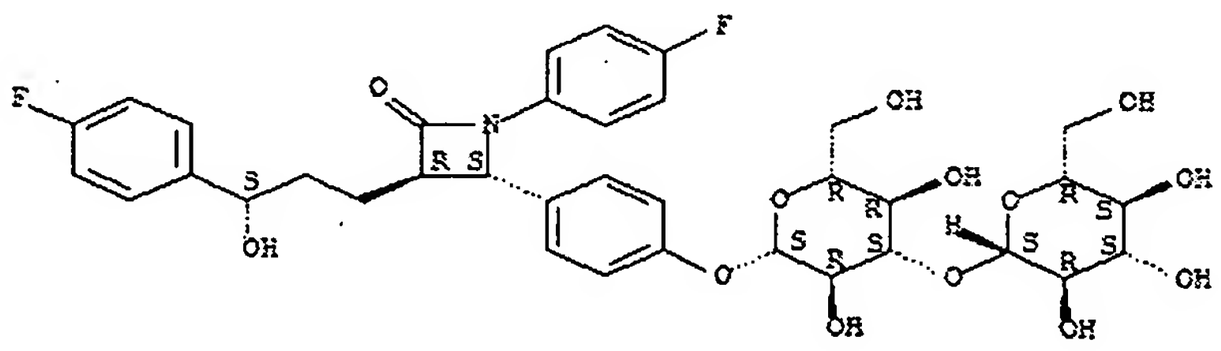


Wherein R^{26} is H or O-sugar, G is a sugar, and Ar^1 and Ar^2 are aryl or substituted aryl. Specific embodiments are claimed in claim 13 and include, among others, the following:

L2 ANSWER 3 OF 45 REGISTRY COPYRIGHT 2008 ACS on STN
RN 208259-77-2 REGISTRY

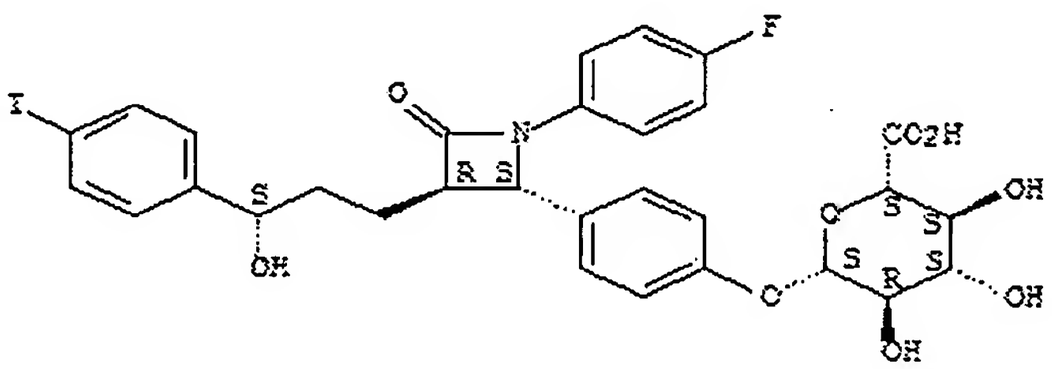
ED Entered STN: 09 Jul 1998
CN 2-Azetidinone, 1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-[(3-O-β-D-glucopyranosyl-β-D-glucopyranosyl)oxy]phenyl]-, (3R,4S)- (CA INDEX NAME)
FS STEREOSEARCH
MF C36 H41 F2 N O13
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



L2 ANSWER 11 OF 45 REGISTRY COPYRIGHT 2008 ACS on STN
RN 190448-79-4 REGISTRY
ED Entered STN: 27 Jun 1997
CN β-D-Glucopyranosiduronic acid, 4-[(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-(4-iodophenyl)propyl]-4-oxo-2-azetidinyl]phenyl (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H29 F I N O9
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

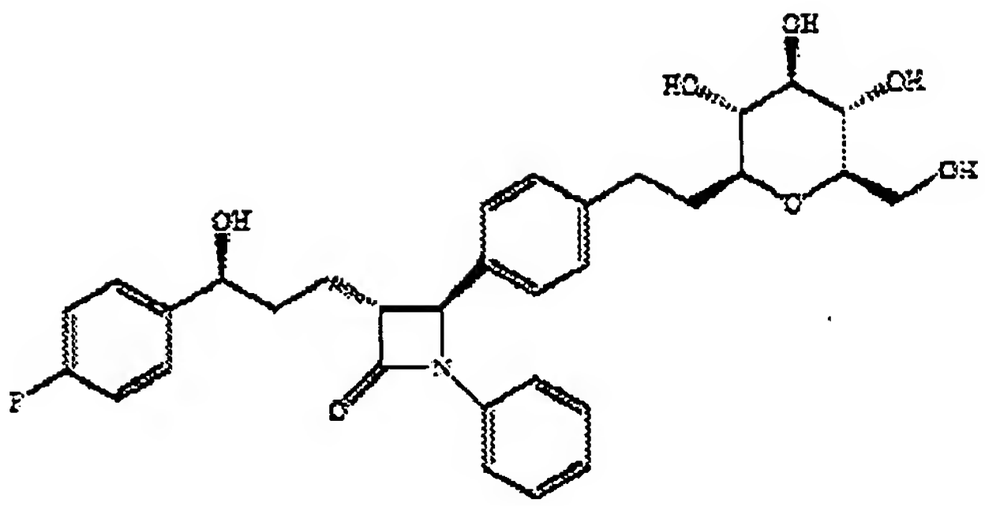
Absolute stereochemistry.



The difference in the beat-lactams taught by Yumibe et al. and the instantly claimed beta-lactams is that the instantly claimed lactams comprise C-glycosides and those of Yumibe et al. comprise O-glycosides.

Tomiyama et al teach beta-lactam compounds which are useful as serum cholesterol lowering agents and which meet the limitations of the instant claims [see abstract and columns 2-3, and structures in columns 7-36]. Tomiyama et al. teach that O-glycoside bonds in beta-lactam-O-glucuronate compounds can be hydrolyzed in the small intestine, possibly reducing the activity of the compounds [column 1, lines 51-62]. Beta-lactams having a C-glycoside, which is stable to metabolism by glycosidase and hydrolysis, were prepared [column 2, lines 3-10]. One preferred compound, compound 56 [column 35], shown below, is the same compound as that which is recited in the instant claim 4:

56



Other preferred compounds include compound 37 [column 25], which is the same compound as that which is recited in instant claim 5.

Tomiyama et al. do not teach a combination of beta-lactam and cholesterol biosynthesis inhibitor.

It would have been obvious to one of ordinary skill in the art to prepare a cholesterol lowering composition of a cholesterol biosynthesis inhibitor and a β-lactam taught by Tomiyama et al. The combination of beta-lactam cholesterol absorption inhibitor and cholesterol biosynthesis inhibitor is already known in the art, as taught by Yumibe et al. Tomiyama et al. teach modified beta-lactmans which are ideal cholesterol absorption inhibitors with low incidence of side effects [column 1, line 65-column 2, line 2]. One of ordinary skill in the art could have substituted Tomiyama's modified beta-lactams for the beta-lactams in the combination taught by Yumibe et al. and would have predicted that the resulting composition would be effective for reducing plasma cholesterol levels and treating atherosclerosis.

Further, both cholesterol biosynthesis inhibitors and the β-lactams taught by Tomiyama et al. are known in the art for reducing serum cholesterol levels. It is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose. In re Kerkhoven, 626 F.2d 846, 205 U.S.P.Q. 1069 (C.C.P.A. 1980)."

The Federal Circuit has ruled that a *prima facie* case of obviousness must establish: (1) some suggestion or motivation to modify the references; (2) a reasonable expectation of success;

and (3) that the prior art references teach or suggest all claim limitations. Amgen, Inc. v. Chugai Pharm. Co., 18 USPQ2d 1016, 1023 (Feb. Cir. 1991); In re Fine, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970).

A *prima facie* case of obviousness must also include a showing of the reasons why it would be obvious to modify the references to produce the present invention. See Ex parte Clapp, 277 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). The examiner bears the initial burden to provide some convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings. Id. at 974.

Applicants respectfully traverse the rejection because the prima *facie case* of obviousness has not been established with respect to the claims as amended herein.

The β-lactam compounds disclosed in Yumibe et al. (U.S. 5,756,470) become active compounds by absorption and metabolism in the intestine and, after transfer to the blood, are secreted into the gastrointestinal tract through bile to inhibit cholesterol absorption in the small intestine, thereby establishing their efficacy in a cholesterol lowering action. (See Margaret van Heek et al., Br. J. Pharmacol. 129, 1748-1754, 2000, lines 22-27 of page 1748, a copy of which is submitted herewith as Exhibit A).

Drug concentrations of β-lactam compounds of Yumibe et al. in the blood are reported to increase approximately 1.5 times

when used together with fibrate type compounds such as fenofibrate as disclosed by Schering-Plough K.K. Zetia prescribing information, lines 29-30 of page 10, a copy of which is submitted herewith as Exhibit B. In addition, the incidence of increase of serum transaminase, which is one of the side effects observed with the single administration of HMG-CoA reductase inhibitor classified as a cholesterol biosynthesis inhibitor, is 0.4%, whereas the incidence of this side effect increases to 1.3% when the β-lactam compounds of Yumibe et al. are administered together with HMG-CoA reductase inhibitors and it is recommend that in such instances liver function tests be carried out at early stages of use (see page 10, lines 1-8 of Exhibit B)

From these facts, it is clear that there is concern about undesirable drug interactions with respect to the pharmacokinetics in blood and the increased side effects of combinations of the β-lactams of Yumibe et al. and fibrate type compounds or cholesterol biosynthesis inhibitors absorbed from the intestine.

In contrast, the β-lactam compounds of Tomiyama et al. (U.S. 2004/0063929) used in the present application, are not absorbed from the intestine, transferred to the blood and reintroduced into the small intestine through bile. Instead, the β-lactams of Tomiyama et al. and the present application remain in the small intestine and display their effect (the lowering of cholesterol

in the blood) by directly inhibiting the absorption of cholesterol in the small intestine. The β-lactam compounds used in the present invention have the characteristic that they are not present in the blood and therefore do not affect the pharmacokinetics in the blood of fibrate-type compounds or cholesterol biosynthesis inhibitors (see Par. 0004 of Tomiyama et al.).

Accordingly, the β-lactam compounds of Yumibe et al and those of Tomiyama et al. exhibit completely different behavior *in vivo* with one requiring activation by absorption into the blood and reintroduction to the small intestine while the other remains in the small intestine and is directly active therein. The clear result of this different behavior is a difference in the pharmacokinetics in the blood when the respective β-lactams are combined with fibrate-type compounds or cholesterol biosynthesis inhibitors.

Applicants respectfully submit that this difference in behavior of the β-lactams of Yumibe et al. and Tomiyama et al. would not influence one of ordinary skill in the art to modify Tomiyama et al. by combining the β-lactams thereof with the cholesterol biosynthesis inhibitor of Yumibe et al. since there is nothing to suggest such a combination with the C-glycoside β-lactams of Tomiyama et al. Since the O-glycoside β-lactams of Yumibe et al. are known to exhibit undesirable side effects in combination with fibrate-type compounds or cholesterol

biosynthesis inhibitors, one would endeavor to avoid such side effects by avoiding similar combinations. It was not until the present application that Applicants discovered that fibrate-type compounds and cholesterol biosynthesis inhibitors could be used with the C-glycoside β-lactams disclosed by Tomiyama et al.

It is a tenet of patent law that an invention that otherwise might be viewed as an obvious modification of the prior art will not be deemed obvious in a patent law sense when one or more prior art references "teach away" from the invention. *Chisum on Patents*, §5.03[3][a][i][G]. In *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303, 310 (Fed. Cir. 1983), the Federal Circuit found that the District Court had erred "in considering the references in less than their entireties, i.e., in disregarding disclosures in the references that diverge from and teach away from the invention at hand.", citing *In re Kuderna*, 165 USPQ 575 (CCPA 1970). Prior art references must be considered in their entireties in an obviousness inquiry and must include a "full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *American Standard, Inc. v. Pfizer, Inc.*, 15 USPQ 2d 1673, 1706 (D.C. Del. 1989). Although each reference used in an obviousness inquiry does not have to be enabling, disclosures in the references that "teach away" from the claimed invention cannot be disregarded. *American Standard, Inc.*, 14 USPQ 2d at 1707, citing *W.L. Gore*.

A prior art reference may be considered to teach away when:

> "a person of ordinary skill upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."

Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH, 45 USPQ 2d 1977, 1984, citing *In re Gurley*, 31 USPQ 2d 1130, 1131 (Fed. Cir. 1994). There is no suggestion to combine however if a reference teaches away from its combination with another source. *Tec Air, Inc. v. Denso Manufacturing Michigan, Inc.*, 52 USPQ 2d 1294, 1298 (Fed. Cir. 1999).

Tomiyama et al. "teach away" from Yumibe et al., given the fact that O-glycoside β-lactams such as disclosed by Tomiyama et al. are known to exhibit undesirable side effects in combination with fibrate-type compounds or cholesterol brosynthesis inhibitors such as disclosed by Yumibe et al. As such, the examiner may not disregard the aspects of Tomiyama et al. that teach away from Yumibe et al. *American Standard, Inc.* Given the fact that Tomiyama et al. teach away from Yumibe et al., there is no suggestion to combine them. *Tec Air, Inc.*

Applicants point to the common inventors and ownership of the Tomiyama et al. reference and the present application and note that the present application is an outgrowth of the work commenced in the reference and constitutes an improvement thereon by those with ordinary skill in the art.

To determine the effectiveness of the combinations of the present invention, applicants conducted experiments showing the improvement achieved with the C-glycoside β-lactams of Tomiyama et al. and fibrate-type compounds or biosynthesis inhibitors. These experiments were carried out with hamster models and the results are shown in Tables 13 and 14 of the specification of the present invention.

In the first experiment shown in Table 13, a combined dosage of compound 56 of Tomiyama et al. at 0.3 mg/kg/day was administered with Fenofibrate at 10 mg/kg/day to achieve a reduction in serum cholesterol of 41.3% whereas the sum reduction achieved by individual use of the two agents was, respectively, 6.9% and 10.7% for a total of 17.6%. Further, in the case of a combined dosage of compound 56 at 0.3 mg/kg/day and Atorvastatin at 1 mg/kg/day, the reduction of serum cholesterol achieved was 20.2% which was greater than the sum of individual use of, respectively, 6.9% and 6.2% for a total of 13.1%.

Similarly, the experiment summarized in Table 14 combines a dosage of compound 37 of Tomiyama et al. at 0.3 mg/kg/day with Fenofibrate at 10 mg/kg/day for a reduction of serum cholesterol value of 39.5% as compared to the sum total of the separate agents of 28.7% (18.0% and 10.7% respectively). In a combination of compound 37 with Atorvastatin at a dose of 1 mg/kg/day, the reduction in serum cholesterol achieved was 31.5% as against the

sum total of the separate agents of 24.2% (18.0% and 6.2% respectively.

These experiments clearly show a synergistic pharmacological effect of the combination of C-glycoside β-lactams and fibrate-type compounds or cholesterol biosynthesis inhibitors which is neither taught nor suggested by either Yumibe et al or Tomiyama et al.

In addition, Applicants have conducted further experiments comparing the effect of β-lactam compound 56 of Tomiyama et al. and Ezetimibe, a cholesterol absorption inhibitor of Schering-Plough Pharmaceutical (see page 1 of Exhibit B). In this experiment, hamsters were dosed with the subject compounds respectively once a day for 7 days. After the final day, blood was collected and the liver removed. Cholesterol concentration in the blood was measured and HMG-CoA reductase activity was measured using a microsome prepared from the liver. The results are summarized in the following table:

Compound	Amount of dosage (mg/kg)	Reduction ratio of cholesterol in blood	Increasing magnification of HMG-CoA reductase
Compound 56	1	43.5%	5.3(1.8)*
Ezetimibe	0.3	42.8%	3.0
Compound 56	10	32.7%	7.2(2.1)*
Ezetimibe	3	36.9%	3.4

* value in () indicates ratio to increasing magnification of Ezetimibe

From the above results it can be seen that when β-lactam compound 56 of Tomiyama et al (KT6-971) is compared with Ezetimibe there is a similar cholesterol reducing function between the two compounds. However, Compound 56, a C-glycoside β-lactam common to Tomiyama et al. and the present application, exhibits an increased HMG-CoA reductase activity over that of Ezetimibe. The fact that there is an increase in the HMG-CoA reductase activity indicates that even though the two cholesterol absorption inhibitors are the same kind of lactam compound, their action *in vivo* is different and their effects, when used in combination with an HMG-CoA reductase inhibitor are different.

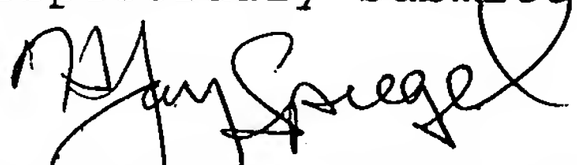
It is thought that the difference in the above effect is due to Ezetimibe being absorbed from the intestine, like the β-lactams of Yumibe et al. while Compound 56 of Tomiyama et al. is not absorbed. Accordingly, Applicants respectfully submit that, although the respective β-lactams may exhibit similar activity on their own, the synergistic response exhibited by a combination of the C-glycoside β-lactams of Tomyiyama, et al., and fibrate-type compounds or cholesterol biosynthesis inhibitors would not be readily apparent from the teachings of the references, especially as the effect of the combination of the β-lactams of Tomiyama et al and fibrate-type compounds or cholesterol biosynthesis inhibitors is pharmacological, while that of the β-lactams of Yumibe et al. and fibrate-type compounds or cholesterol biosynthesis inhibitors is pharmacokinetic.

In view of the foregoing, Applicants respectfully submit that it would not be obvious to one of ordinary skill in the art, knowing the action of the compounds of Yumibe et al. to expect the improvements exhibited by combining the fibrate-type compounds or cholesterol biosynthesis inhibitors of Yumibe et al. with the C-glycoside β-lactams of Tomiyama et al. Because the actions of the β-lactams of the respective references are different, although the ultimate effects are similar, Applicants respectfully submit that there is nothing in either reference to support the combination thereof as urged by the examiner and that a *prima facie* case of obviousness has not been established.

Accordingly, Applicants respectfully submit that the present rejection under 35 U.S.C. 103(a) is without support and should be withdrawn.

In view of the foregoing, Applicants respectfully submit that the claims as amended herein are allowable over the prior art and a notice of allowance is respectfully requested.

Respectfully submitted,



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British Journal of Pharmacology (2000) 129, 1748–1754
www.nature.com/bjp

Comparison of the activity and disposition of the novel cholesterol absorption inhibitor, SCH58235, and its glucuronide, SCH60663

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EXHIBIT A

1 Previous studies described the metabolism-based discovery of a potent, selective inhibitor of intestinal absorption of cholesterol, SCH58235 (Ezetimibe). Here we demonstrate that the phenolic glucuronide (SCH60663) of SCH58235, was more potent at inhibiting cholesterol absorption in rats than SCH58235, when administered by the intraduodenal route.

2 To understand the increased potency of the glucuronide, the metabolism and distribution of SCH58235 and SCH60663 were studied in bile duct-cannulated rats.

3 One minute after intraduodenal delivery of SCH58235, significant levels of compound were detected in portal plasma; >95% was glucuronidated, indicating that the intestine was metabolizing SCH58235 to its glucuronide. When intraduodenally delivered as SCH58235, the compound was glucuronidated, moved through the intestinal wall, into portal plasma, through the liver, and into bile. However, when delivered as SCH60663, >95% of the compound remained in the intestinal lumen and wall, which may explain its increased potency. Significant inhibition of cholesterol absorption and glucuronidation of SCH58235 occurred when SCH58235 was intravenously injected into bile duct-cannulated rats. Autoradiographic analysis demonstrated that drug related material was located throughout the intestinal villi, but concentrated in the villus tip.

4 These data indicate that (a) SCH58235 is rapidly metabolized in the intestine to its glucuronide; (b) once glucuronidated, the dose is excreted in the bile, thereby delivering drug related material back to the site of action and (c) the glucuronide is more potent than the parent possibly because it localizes to the intestine. Taken together, these data may explain the potency of SCH58235 in the rat (ID_{50} = 0.0015 mg kg^{-1}) and rhesus monkey (ID_{50} = 0.0005 mg kg^{-1}).

British Journal of Pharmacology (2000) 129, 1748–1754

Keywords: Cholesterol absorption; plasma cholesterol; intestine; inhibition; intestinal glucuronidation; enterohepatic circulation

Abbreviations: AAALAC, American Association for Accreditation of Laboratory Animal Care; ACAT, acyl-CoA:cholesterol acyltransferase; HMG-CoA, hydroxymethylglutaryl coenzyme A; ID_{50}, dose at which 50% inhibition occurs; LDL, low density lipoprotein, MW, molecular weight; RP-HPLC: reversed phase-high performance liquid chromatography; SCH58235 (Ezetimibe) ((1-(4-fluorophenyl)-(3R)-[3-(4-fluorophenyl)-(3S)-hydroxypropyl]-(4S)-(4-hydroxyphenyl)-2-azetidinone); TLC, thin-layer chromatography

Introduction

It has been well established that elevated plasma cholesterol is positively associated with the incidence of cardiovascular disease (National Research Council, 1989). Evidence is mounting from clinical trials that reducing plasma cholesterol by dietary and/or pharmacological means leads to reductions in the incidence of death from vascular events (4S, 1994; Shepherd *et al.*, 1995; Sacks *et al.*, 1996; LIPID, 1998). Plasma cholesterol is predominantly derived from biosynthesis and dietary intake of cholesterol. Present pharmacological interventions include the inhibition of cholesterol biosynthesis by inhibiting HMG CoA reductase (the statins) either alone or in combination with other agents such as cholestyramine, which sequesters bile acids. In contrast, research efforts have thus far failed to develop pharmacological agents that are selectively targeted towards inhibiting the absorption and traversal of cholesterol through the intestinal wall.

We have previously reported the discovery of a novel class of intestinal cholesterol absorption inhibitors, which have been shown to be selective and potent cholesterol-lowering agents in cholesterol-fed hamsters, rats, rabbits, dogs and cynomolgus and rhesus monkeys (Burnett *et al.*, 1994; Salisbury *et al.*, 1995; Sybertz *et al.*, 1995; van Heek *et al.*, 1997; Rosenblum *et al.*, 1998). We have also shown that compounds of this series are synergistic with a number of the statins (Davis *et al.*, 1994; 1995). The first compound of the cholesterol absorption inhibitors to go into clinical trials, SCH48461, reduced LDL by 15% in humans (Bergman *et al.*, 1995). SCH58235 (Ezetimibe) was shown to be 400 times more potent than SCH48461 in the cholesterol-fed rhesus monkey and is rapidly progressing in clinical trials.

The cholesterol absorption inhibitors prevent the absorption of cholesterol by inhibiting the traversal of dietary and biliary cholesterol across the intestinal wall. The molecular mechanism by which this class of compounds inhibits cholesterol absorption, however, remains unknown and is being intensively investigated at Schering-Plough Research Institute. Previous experiments indicated that ACAT, pancreatic lipase, and HMG-CoA reductase are not potently inhibited by these compounds (Salisbury *et al.*, 1995). The cholesterol absorption inhibitors do not sequester or precipitate cholesterol. These compounds also

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REFERENCE DOCUMENT 2

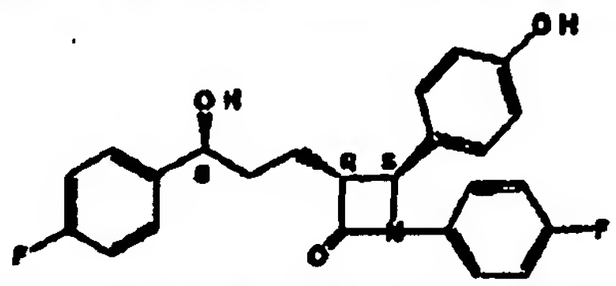
25751841T
REV 03

EXHIBIT B

ZETIA®
(EZETIMIBE)
TABLETS

DESCRIPTION

ZETIA (ezetimibe) is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.4 and its structural formula is:



Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Ezetimibe has a melting point of about 163°C and is stable at ambient temperature. ZETIA is available as a tablet for oral administration containing 10 mg of ezetimibe and the following inactive ingredients: croscarmellose sodium NF, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, povidone USP, and sodium lauryl sulfate NF.

CLINICAL PHARMACOLOGY

Background

Clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C) and apolipoprotein B (Apo B), the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of high density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

ZETIA reduces total-C, LDL-C, Apo B, and TG, and increases HDL-C in patients with hypercholesterolemia. Administration of ZETIA with an HMG-CoA reductase inhibitor is effective in improving serum total-C, LDL-C, Apo B, TG, and HDL-C beyond either treatment alone. The effects of ezetimibe given either alone or in addition to an HMG-CoA reductase inhibitor on cardiovascular morbidity and mortality have not been established.

Mode of Action

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. In a 2-week clinical study in 18 hypercholesterolemic patients, ZETIA inhibited intestinal cholesterol absorption by 54%, compared with placebo. ZETIA had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E (in a study of 113 patients), and did not impair adrenocortical steroid hormone production (in a study of 118 patients).

The cholesterol content of the liver is derived predominantly from three sources. The liver can synthesize cholesterol, take up cholesterol from the blood from circulating lipoproteins, or take up cholesterol absorbed by the small intestine. Intestinal cholesterol is derived primarily from cholesterol secreted in the bile and from dietary cholesterol.

Ezetimibe has a mechanism of action that differs from those of other classes of cholesterol-reducing compounds (HMG-CoA reductase inhibitors, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols).

In controlled clinical combination studies of ZETIA initiated concurrently with an HMG-CoA reductase inhibitor, the incidence of consecutive elevations (≥3 X ULN) in serum transaminases was 1.3% for patients treated with ZETIA administered with HMG-CoA reductase inhibitors and 0.4% for patients treated with HMG-CoA reductase inhibitors alone. Those elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. When ZETIA is co-administered with an HMG-CoA reductase inhibitor, liver function tests should be performed at initiation of therapy and according to the recommendations of the HMG-CoA reductase inhibitor.

Skeletal Muscle

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ZETIA compared with the relevant control arm (placebo or HMG-CoA reductase inhibitor alone). However, myopathy and rhabdomyolysis are known adverse reactions to HMG-CoA reductase inhibitors and other lipid-lowering drugs. In clinical trials, the incidence of CPK >10 X ULN was 0.2% for ZETIA vs 0.1% for placebo, and 0.1% for ZETIA co-administered with an HMG-CoA reductase inhibitor vs 0.4% for HMG-CoA reductase inhibitors alone.

Hepatic Insufficiency

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ZETIA is not recommended in these patients. (See CLINICAL PHARMACOLOGY, *Special Populations*.)

Drug Interactions (See also CLINICAL PHARMACOLOGY, *Drug Interactions*)

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be reduced by this interaction.

Fibrates: The safety and effectiveness of ezetimibe administered with fibrates have not been established.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see ANIMAL PHARMACOLOGY). Co-administration of ZETIA with fibrates is not recommended until use in patients is studied.

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold.

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold.

HMG-CoA Reductase Inhibitors: No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, or fluvastatin.

Cyclosporine: Caution should be exercised when initiating ezetimibe in patients treated with cyclosporine due to increased exposure to ezetimibe. This exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe. In a pharmacokinetic study in post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of >50 mL/min), concomitant cyclosporine administration increased the mean AUC and C_{max} of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively. In a separate study, the total ezetimibe exposure increased 12-fold in one renal transplant patient with severe renal insufficiency receiving multiple medications, including cyclosporine (see CLINICAL PHARMACOLOGY, *Drug Interactions*).

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the *in vivo* mouse micronucleus test.